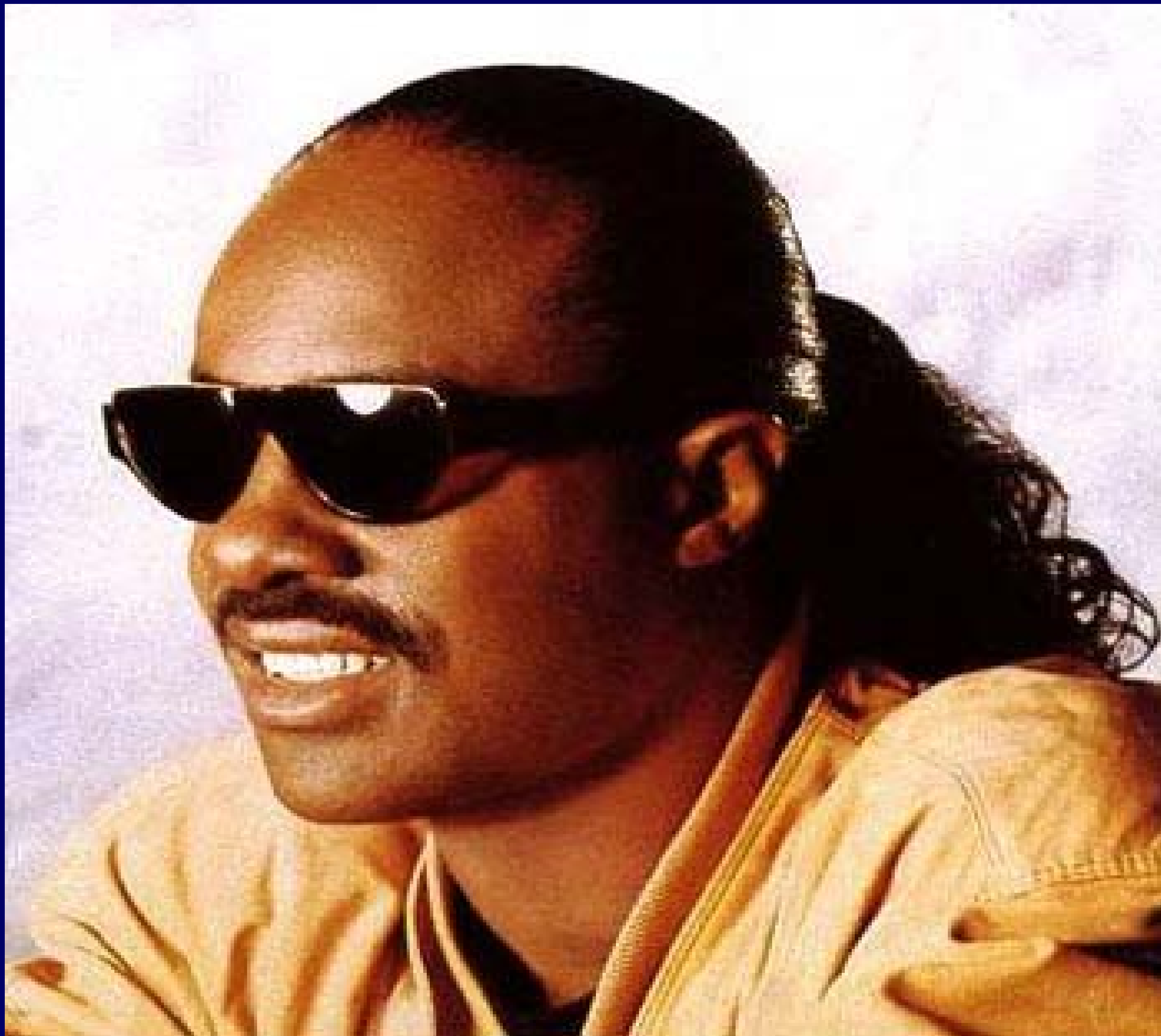
Rango de saturacion de oxigeno: ¿Cual es la evidencia?

Wally Carlo, M.D.
University of Alabama at Birmingham
Department of Pediatrics
Division of Neonatology
wcarlo@peds.uab.edu

Stevie Wonder



Objectives

1. Know the results of the SUPPORT RCT arm of lower versus high oxygen saturation targeting
2. Be able to apply the results of this trial in your daily practice

Background

- No consensus on targets
- Published "acceptable" levels in neonates are 88-98%
- No standards on assessing "need" in infants
- In contrast, supplemental O_2 "need" assessment is standard in COPD patients

What PaO_2 or SaO_2 should we target?

Does the oxygenation targeting matter?

Recent Trials of Oxygenation Targets

STOP-ROP Trial

BOOST Trial

SUPPORT Trial

SaO_2 Targets: STOP-ROP Trial

Methods

Design:	Multicenter RCT, not masked
Patient population:	649 preterm infants with prethreshold ROP
Treatment group:	O_2 sat 96-99% or 89-94%
Primary outcome:	Progression to threshold ROP in at least one eye

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: STOP-ROP Trial

	Sats 96 to 99%	Sats 89 to 94%	p value
Threshold ROP	41%	48%	<0.05
Pneumonia/BPD exacerbations	13%	8%	= 0.07
Prolonged hospitalization*	13%	7%	<0.05
Prolonged oxygen*	47%	37%	<0.05
Prolonged diuretics*	36%	24%	<0.05
Death	3%	2%	NS

* At 3 months corrected age

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: BOOST Trial

Methods

Design:	Multicenter RCT, double blind
Patient population:	358 infants born at < 30 weeks and oxygen dependent at 32 weeks
Treatment groups:	SaO_2 95-98% or 91-94%
Primary outcome:	Growth and neurodevelopment at 12 months corrected age

Askie et al. NEJM 349:959, 2003

SaO_2 Targets: BOOST Trial

	Sats 95-98%	Sats 91-94%	p value
Dev abnormality	23%	24%	NS
Weight < 10% tile	33%	37%	NS
Death	5%	3%	NS
O_2 at 36 w	64%	46%	<0.001
Home O_2	30%	17%	<0.001

Askie et al. NEJM 349:959, 2003

Current O_2 Targets and Practice

Design: Prospective multicenter observational study

Patient Population:
- 84 infants <28 week, <96 hours in 14 centers in 3 countries, monitored for 4 weeks
- Birthweight 863 ± 208 grams
- Gestational age 26 ± 1 week

Hagadorn et al. Pediatrics 118:1574, 2006

Current O_2 Targets and Practice

	Targets	Actual
Upper limit	92 to 98%	97% (75 % tile)
Lower limit	83 to 92%	91% (25 % tile)
Range	88%, 95%	95% (median)
Compliance by Center	--	16-64%

Thus, compliance varied widely and was generally poor (50%), and achieved saturations are 34% higher than target

Hagadorn et al. Pediatrics 118:1574, 2006

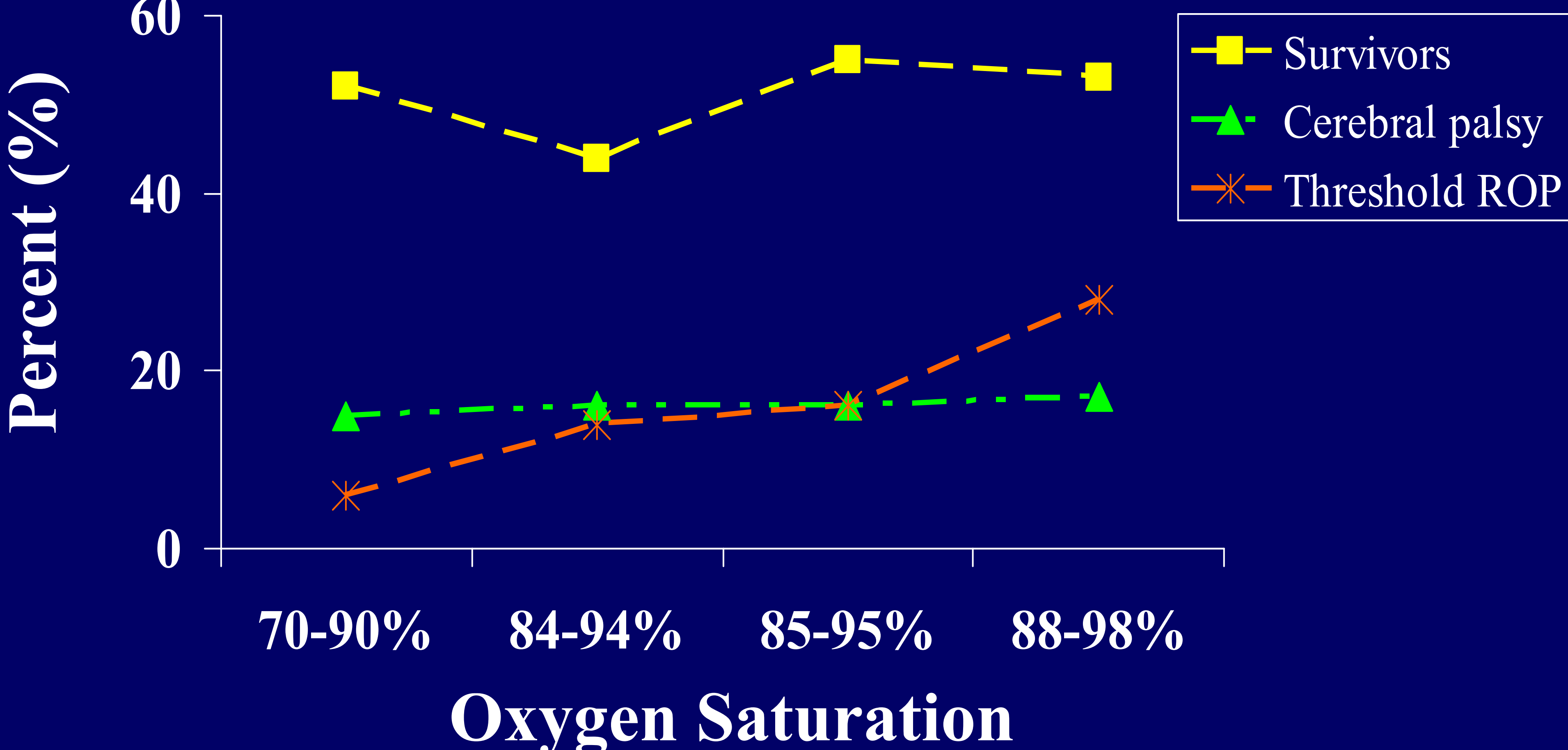
SaO_2 Targets: Retrospective Study

Methods

- Retrospective review
- Population study - All babies < 28 weeks in several referral units
- Data analyzed by SaO_2 targets

Tin et al. Arch Dis Child. 84:F106, 2001

SaO_2 Targets: Retrospective Study



Tin et al. Arch Dis Child. 84:F106, 2001

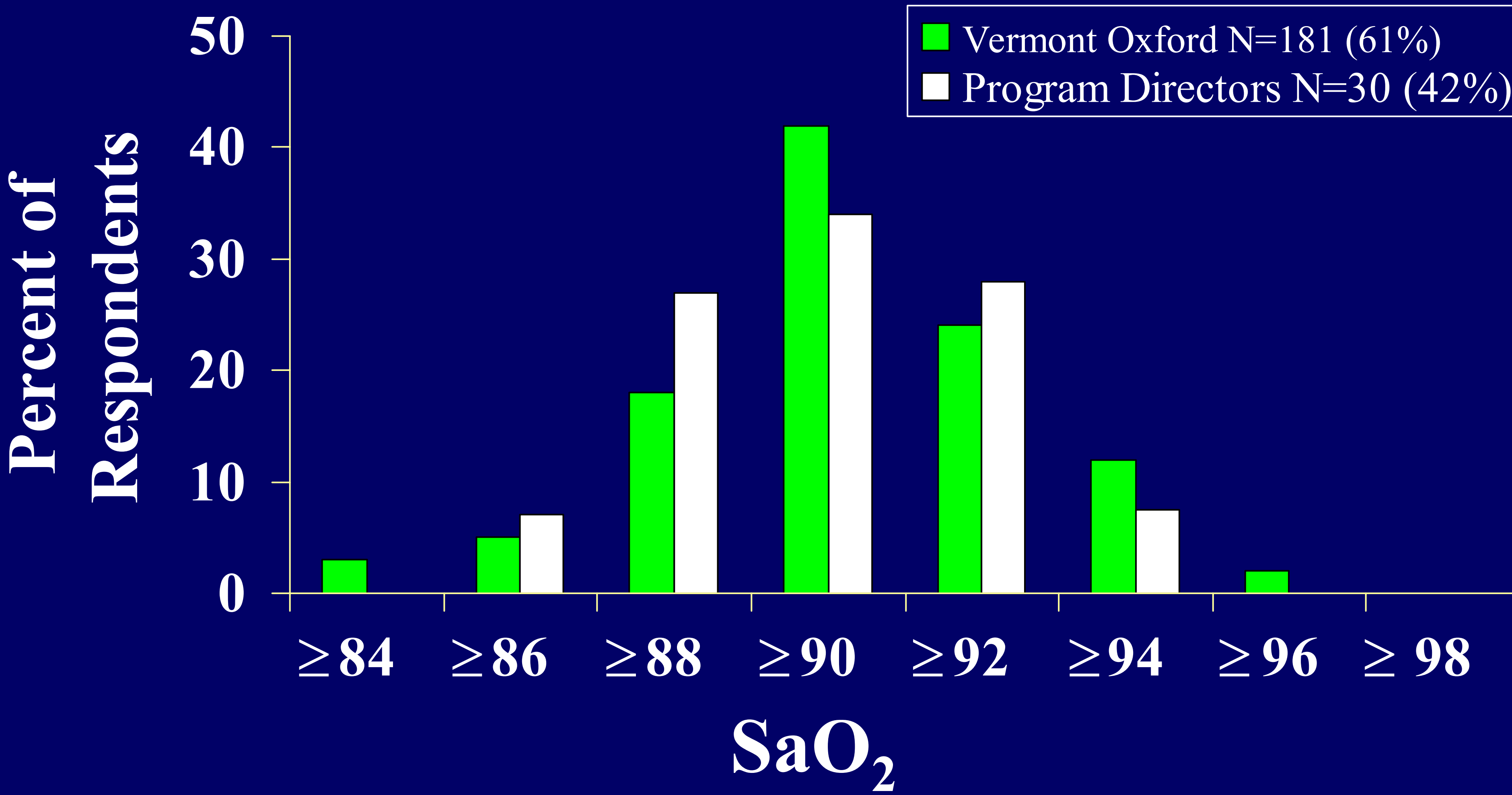
SaO_2 Targets: Expert Opinion

Methods

Design:	Survey of VON Centers and ONTPD
Respondents:	181 (61%) VON Centers and 30 (42%) PD

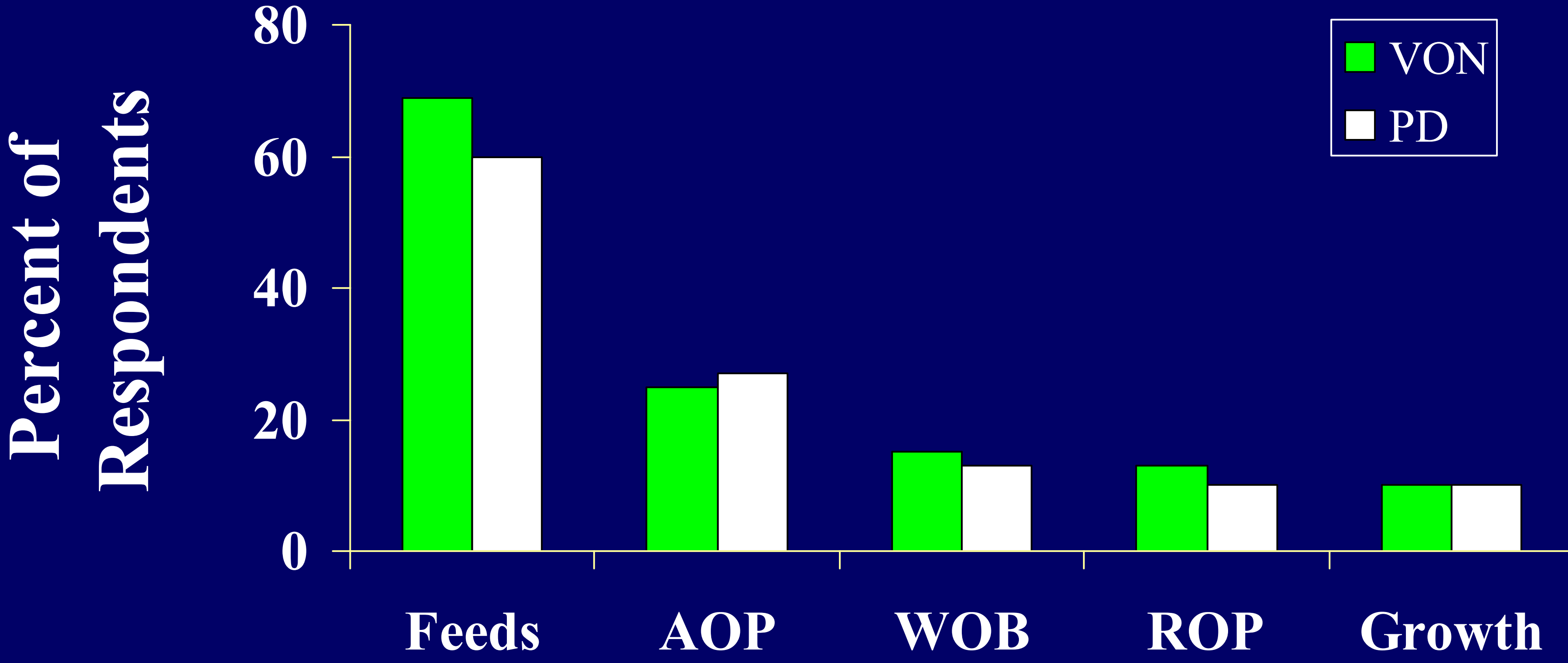
Ellsbury et al. J Pediatr 140:247, 2002

SaO_2 Targets: Expert Opinion



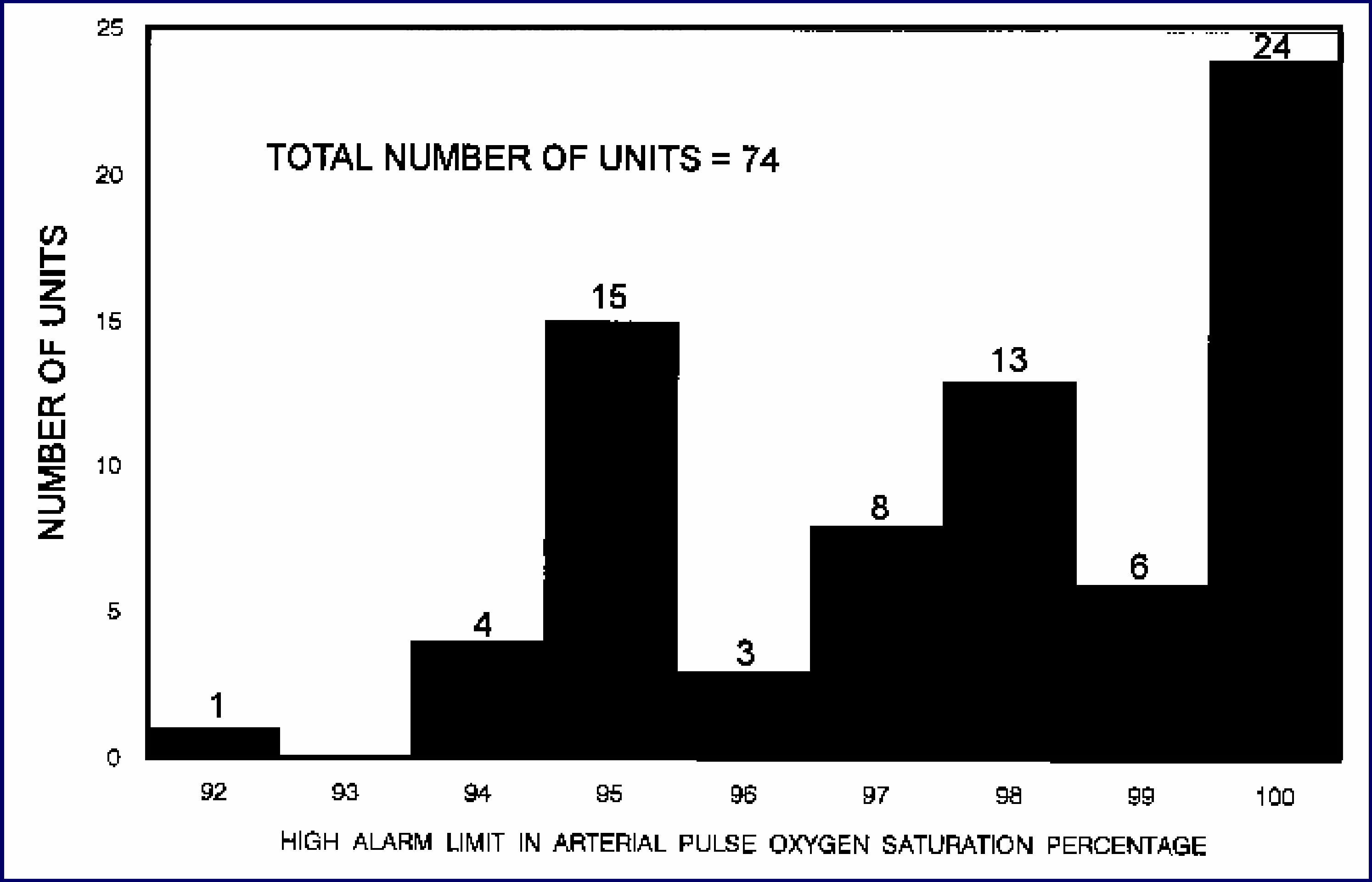
Ellsbury et al. J Pediatr 140:247, 2002

Indications for Supplemental Oxygen



Ellsbury et al. J Pediatr 140:247, 2002

Value at Which High Arterial Pulse Oxygen Saturation Alarm is Set



Vijayakumar et al. J Perinatol 17:341, 1997

Randomized Trial of Oxygen Saturation Targets in Premature Infants - the SUPPORT Trial

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

National Heart Lung and Blood Institute

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

Background

- Retinopathy of prematurity (ROP) continues to be an important cause of blindness in preterm infants
- Recent observational data suggest that oxygen saturations in the lower limits of common clinical practice (83 or 85%) may reduce ROP but this has not been tested in RCTs
- Furthermore, in RCTs of oxygen supplementation to reduce ROP conducted in the 1950s, restriction of oxygen supplementation resulted in an increased mortality in infants in the lower oxygen group

Hypothesis

A lower O_2 saturation target range (85 to 89%)

compared to

a higher O_2 saturation target range (91 to 95%)

reduces

the incidence of the composite outcome of severe ROP or death

among

infants of 24 $^{0/7}$ to 27 $^{6/7}$ weeks gestational age

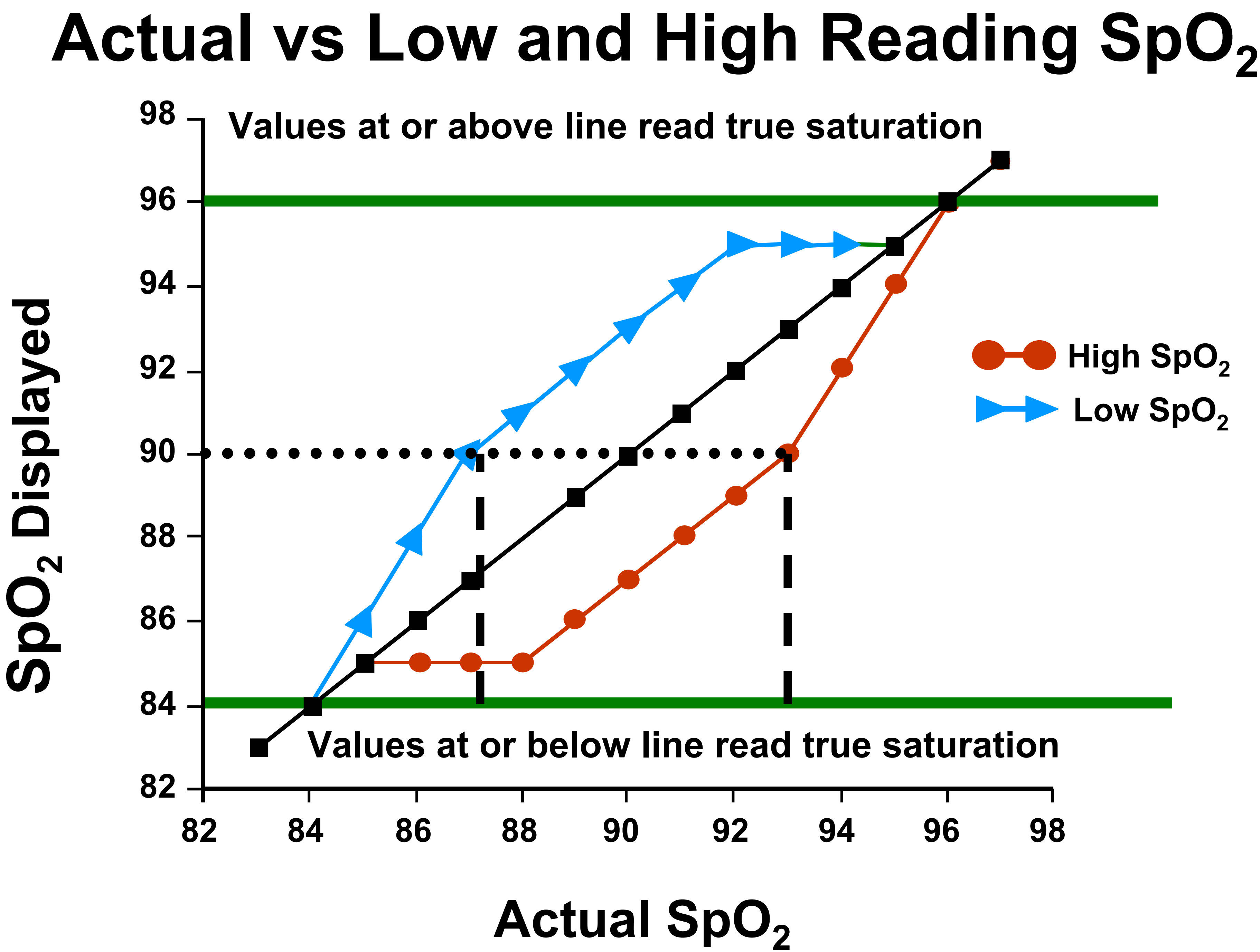
Method – Patients

- Inborn infants of 24 $^{0/7}$ to 27$^{6/7}$ weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment was conducted from February 2005 to February 2009
- Randomization was stratified by center and by gestational age:
  - 24 and 25 weeks
  - 26 and 27 weeks

Methods – Intervention (1)

- Infants were randomized to:
  - lower saturation targeting (85 to 89%) or;
  - higher saturation targeting (91 to 95%)
- Oxygen saturations were monitored with electronically-altered Masimo Radical Pulse Oximeters

SpO_2 Group	Displayed	Actual Target	Alarm Values
Low SpO_2	88-92%	85-89%	<84 and >96%
High SpO_2	88-92%	91-95%	<84 and >96%



Actual vs Low and High Reading SpO_2
Values at or above line read true saturation
Values at or below line read true saturation
High SpO_2
Low SpO_2
SpO_2 Displayed
Actual SpO_2
98
96
94
92
90
88
86
84
82
82
84
86
88
90
92
94
96
98

Recent Trials of Oxygenation Targets

	Experimental	Control
SUPPORT	85-89%	91-95%
STOP-ROP	96-99%	89-94%
BOOST	95-98%	91-94%

Methods – Intervention (2)

- Oxygen saturation targeting was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained on room air and off the ventilator/CPAP for >72 hours, whichever occurred first
- Adjustments in supplemental oxygen to maintain the displayed saturation within the target range of 88 to 92% were performed by the clinical staff, not the researchers

Methods – Factorial Design

Infants were also randomized to CPAP started at birth or intubation with surfactant

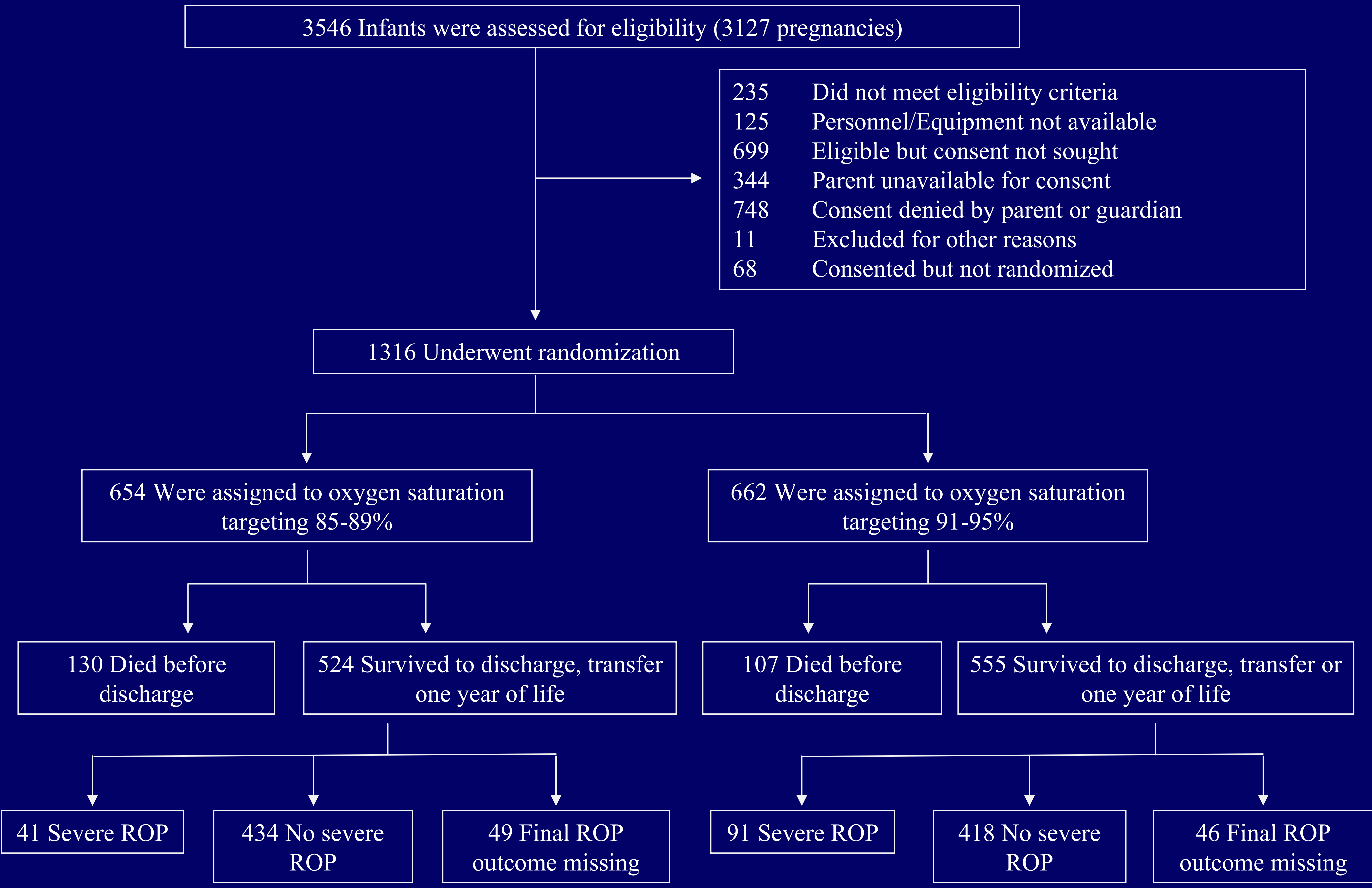
Methods – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint of severe retinopathy *or* fully vascularized retinas *or* immature vessels in zone III for two consecutive exams in each eye were documented

- Severe retinopathy was defined as:
  - threshold retinopathy if any of the following were present:
    - In zone I: stage 3 ROP; plus disease with any stage of ROP or
    - In zone II: plus disease with stage 2 or 3 ROP or
  - If ophthalmologic surgery and/or bevacizumab ROP treatment was used

Methods – Sample Size Monitoring and Analysis

- Based on an absolute difference of 10% in the primary outcome, sample size was 1310
- An independent DSMC reviewed primary outcomes and adverse events at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

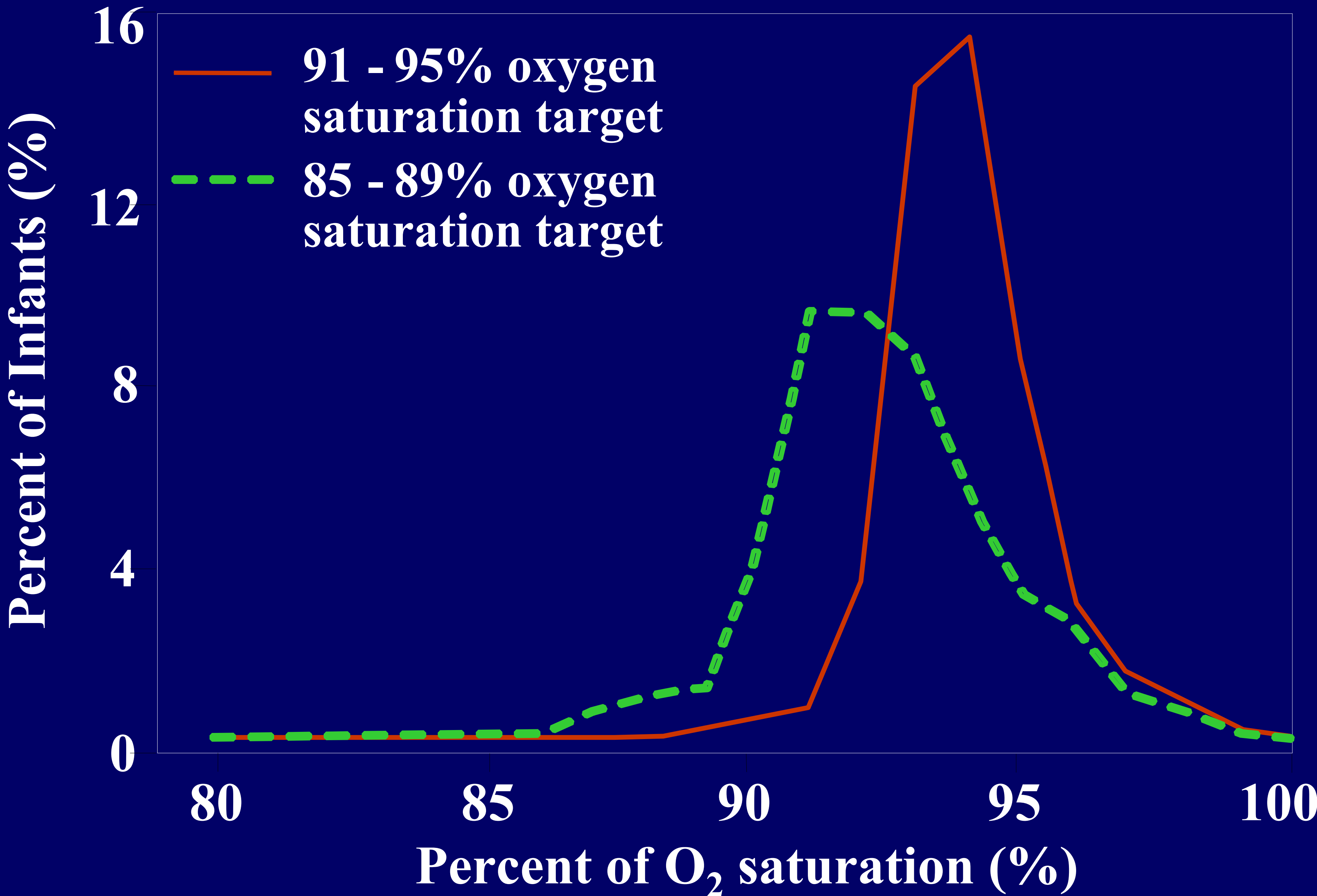

3546 Infants were assessed for eligibility (3127 pregnancies)
235 Did not meet eligibility criteria
125 Personnel/Equipment not available
699 Eligible but consent not sought
344 Parent unavailable for consent
748 Consent denied by parent or guardian
11 Excluded for other reasons
68 Consented but not randomized
1316 Underwent randomization
654 Were assigned to oxygen saturation targeting 85-89%
662 Were assigned to oxygen saturation targeting 91-95%
130 Died before discharge
524 Survived to discharge, transfer one year of life
107 Died before discharge
555 Survived to discharge, transfer or one year of life
41 Severe ROP
434 No severe ROP
49 Final ROP outcome missing
91 Severe ROP
418 No severe ROP
46 Final ROP outcome missing

Results – Patient Population*

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birth weight	836±193 grams	825±193 grams
Gestational age	26±1 weeks	26±1 weeks
Race, White/Black/Hispanic	37/39/20%	42/35/19%
Antenatal corticosteroids	96.8%	95.6%
Multiple births	24.6%	26.6%

*All p values >0.05

Actual Median Oxygen Saturation (%)



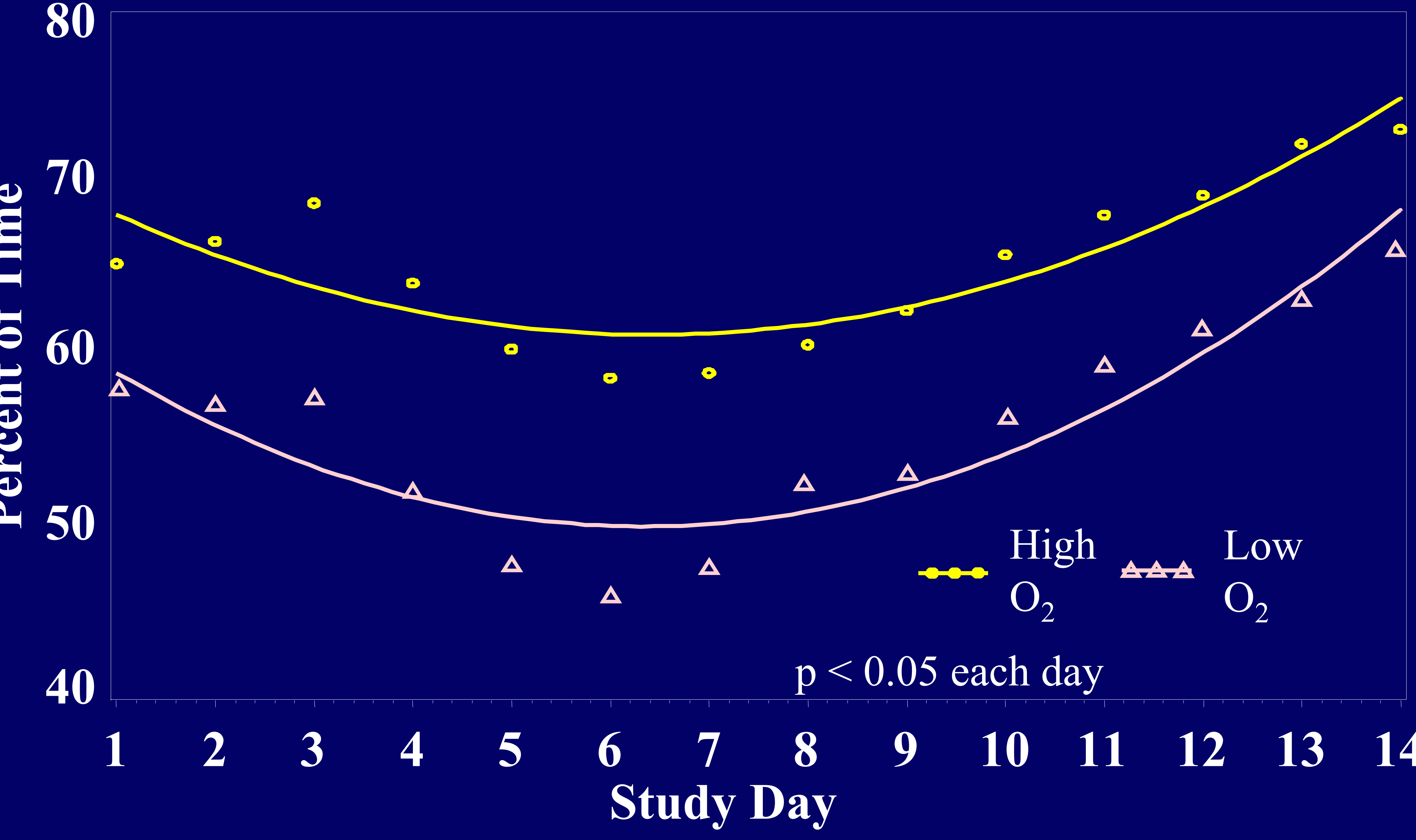
Mean Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Mean % of time in range (95% CI)	Higher Saturation Group Mean % of time in range (95% CI)	p value
>96%	20.1 (18.8, 21.3)	23.2 (22.0, 24.5)	0.001
<85%	7.3 (6.6, 8.1)	5.5 (4.8, 6.3)	0.001
<75%	4.5 (3.8, 5.2)	3.6 (2.9, 4.3)	0.049
<70%	2.5 (1.9, 3.1)	2.1 (1.5, 2.7)	0.409

Median Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Median % of time in range	Higher Saturation Group Median % of time in range	p value
>96%	16.0	19.6	<0.001
<85%	5.9	3.9	<0.001
<75%	3.3	2.1	<0.001
<70%	1.5	0.9	<0.001

Percent of Time on Oxygen by Day and Group



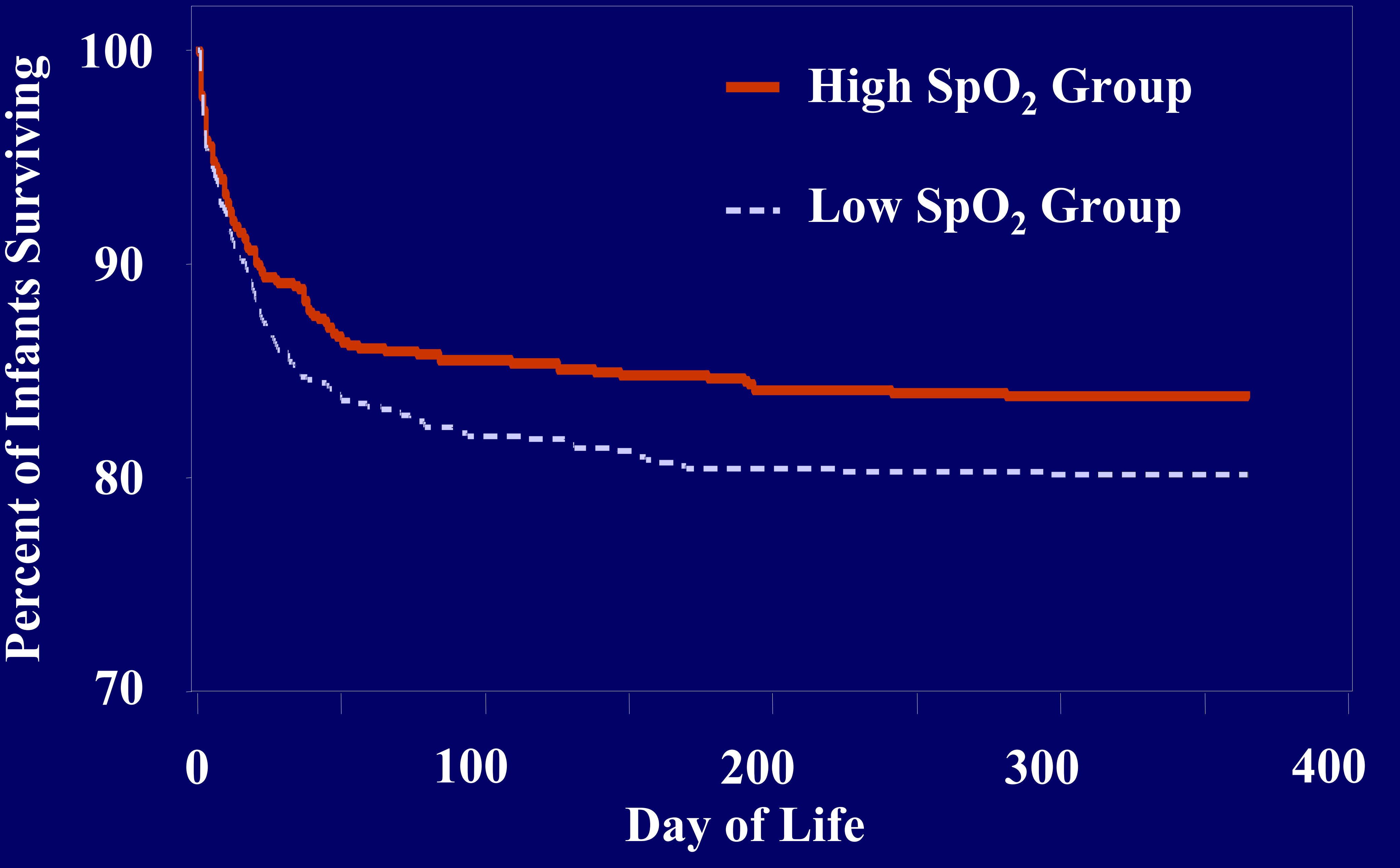
Results – Primary Outcome

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)	
Severe ROP/death	28.3%	32.1%	0.90 (0.76, 1.06)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Death	19.9%	16.2%	1.27 (1.01, 1.60)	NNH=27

Results – ROP Adjudication Analysis

	Lower Saturation Group N=654	Higher Saturation Group N=662	Relative Risk for Low SpO_2 vs. High SpO_2 (95% CI)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Severe ROP with adjudication (98.6%)	8.0%	16.6%	0.52 (0.37, 0.73)	NNT=12
Severe ROP with ROP if lost to F/U (100%)	10.1%	17.5%	0.62 (0.45, 0.84)	NNT=14

Survival Curve



Results – BPD and Other Pulmonary Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
BPD (O_2 use at 36 w)	37.6%	46.7%	0.82 (0.72, 0.93)
BPD (O_2 use) or death, 36 w	48.5%	54.2%	0.91 (0.83, 1.01)
BPD (phys), 36 w	38.0%	41.7%	0.92 (0.81, 1.05)
BPD (phys) or death, 36 w	48.8%	50.0%	0.99 (0.90, 1.10)
Pneumothorax	7.2%	6.5%	1.12 (0.74, 1.68)
Any air leaks (14 days)	7.8%	6.3%	1.23 (0.83, 1.83)
Postnatal steroids for BPD	9.6%	10.7%	0.91 (0.67, 1.24)

Results – PDA

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
PDA	47.9%	50.0%	0.96 (0.86, 1.07)
Medical R_x for PDA	34.5%	36.1%	0.95 (0.82, 1.09)
Surgical R_x for PDA	11.4%	10.5%	1.09 (0.80, 1.48)

Results – Other Major Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
IVH, grade 3 or 4	13.2%	12.7%	1.06 (0.80, 1.40)
PVL	3.8%	4.7%	0.83 (0.49, 1.42)
NEC, stage ≥ 2	11.9%	10.8%	1.11 (0.82, 1.51)
Late onset sepsis	36.5%	35.6%	1.03 (0.89, 1.18)

Summary

- O_2 saturation targeting in the range of 85-89% did not affect severe ROP/death
- O_2 saturation targeting in the range of 85-89% resulted in a significant reduction in severe ROP (17.9 to 8.6%, NNT = 11)
- However, mortality was significantly increased in the 85-89% target group (19.9 versus 16.2%, NNH = 27)

Conclusions

- Lower oxygen saturation targeting, as conducted in this trial, did not reduce severe ROP/death
- Lower oxygen saturation targeting, as conducted in this trial, decreased severe ROP
- The potential to reduce the risk of severe ROP must be carefully weighed against the possibility of increased risk of death
- Follow up of these infants and data from the similarly designed ongoing trials will be important

Take Home Message

- Current SaO_2 targets and high alarm limits are too high
- Most current data suggest that oxygen saturation in the low 90s is sufficient to preterm infants
- Additional oxygen supplementation increases ROP and may worsen pulmonary outcomes
- Lower oxygen supplementation may increase the risk for mortality

Consider Changes in Practice

- Use high saturation alarm at 95% if the baby is on oxygen supplementation and at 99% if the baby is on room air, but at risk for getting oxygen.
- Do physiologic assessment of oxygen "needs" as daily practice.

Thanks to the many infants, parents, and NICU staff

Thanks to the members of the Neonatal Research Network

NICHD Neonatal Research Network Centers (2005-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development